

## REMARKS

### Election/ Restriction Requirement and claims currently under consideration

Applicants have elected Group II (induction of cardiomyogenesis) to be searched and examined; claims to the methods of Groups I, III and IV are canceled.

With regard to the species election, applicants request that claims which recite non-elected species be examined if the elected species are found to be free of the prior art of record.

### Amendments to the claims

Some of the claims have been amended to address points raised by the Examiner and/or to clarify aspects of the invention. The amendments are fully supported by the specification and do not add new matter. *The amendments were made in order to place the application in condition for allowance. Therefore, it is respectfully requested that this after-final amendment be entered and considered.*

Some of the claims (e.g. claims 1 and 33) have been amended to delete the recitation of arteriogenesis, lymphangiogenesis or vasculogenesis, without prejudice or disclaimer. Applicants reserve the right to pursue prosecution of these embodiments of the invention in a continuation application.

Some of the claims (e.g. claims 1 and 65) have been amended to delete the recitation of an active site of the VEGF; and dependent claims directed to these embodiments of the invention (e.g. claims 26 and 27) have been canceled, without prejudice or disclaimer. Applicants reserve the right to pursue prosecution of these embodiments of the invention in a continuation application.

Some of the claims (e.g. claim 43) have been amended to clarify that the method of delivery of the plasmid is intramyocardial administration (the elected species for route of administration), e.g. by transpericardial administration or by transendocardial administration. Claims directed to other means of administration (e.g. claims 37-42 and 45-47 have been canceled, without prejudice or disclaimer. Applicants reserve the right to pursue prosecution of these embodiments of the invention in a continuation application.

Other claims have been amended to correct claim dependency or to eliminate duplicative claims, to be consistent with the claims as currently amended.

The amendment to claim 34 is supported, *e.g.*, at page 6, lines 3-5 of the specification.

In addition to the claims which have been previously canceled, claims 3-9, 26-27, 37-42, 45-50, 57-58, 100-101 have been canceled. Thus, claims 3-9, 15-18, 26-30, 32, 37-42, 45-50, 57-58, 63, 67-68, 70, 81-97 and 100-101 have been canceled.

New claim 105 is fully supported by the specification. For example, Example V shows that administration of a dose of the plasmid that is effective to induce cardiomyogenesis also results in the induction of arteriogenesis.

Claims 1, 2, 10-14, 19-25, 31, 33-36, 43-44, 51-56, 59-62, 64-66, 69, 71-80, 98-99 and 102-105 are currently under consideration.

#### Claim objection

Amended claim 1, which was objected to as being directed to a non-elected invention, now recites a method for inducing cardiomyogenesis, which is the elected embodiment of the invention.

#### Enablement rejections

The Examiner alleges that "active sites" of VEGF 1-165 are not adequately enabled by the specification. Applicants disagree, for reasons of record. Nevertheless, in an effort to expedite prosecution, claims 1 and 65 have been amended to delete the recitation of "active site."

The Examiner alleges that the claimed methods of delivery do not allow for selective targeting of cells *in vivo*, and thus are not adequately enabled for this purpose by the specification. Applicants disagree, for reasons of record. Nevertheless, in an effort to expedite prosecution, the claims (*e.g.*, claim 43) have been amended to clarify that the method of delivery is intramyocardial administration (direct administration to the myocardium), and that this can be accomplished either by (1) transpericardial administration (injection into the heart muscle during surgery) or by (2) transendocardial administration (using a catheter to introduce the plasmid into heart muscle). In either of these methods, the plasmid is introduced directly into the target cardiomyocyte cell or tissue comprising cardiomyocytes, thereby obviating the delivery problems alleged by the Examiner to be problematic.

The Examiner alleges that applicants' referral to the Vera Janavel publication of 2006 (Vera Janavel *et al.* (2006) *Gene Therapy* 13, 1133-42) does not contribute to the enablement of the claims, because the paper was published after the filing date of the application. This allegation is unjustified. In the first place, the data presented in the application as filed, using the pig model, show that a gene therapy method of the present claims results in at least arteriogenesis and cardiomyogenesis. See, *e.g.*, Example V. This disclosure alone is sufficient to enable the claims. Furthermore, and supplementally, in Example VI, starting on the bottom of page 35 of the U.S. C.I.P., the application states that "Plasmids as above have also been introduced into sheep suffering from acute myocardial infarction, and myocardiogenesis has been observed. The methods in this study were adapted from methods used in the preceding Examples." The Vera Janavel (2006) paper was provided to the Examiner merely to supplement and enlarge upon the (already enabling) statement made in the patent application. Thus, the paper should not be considered to be "post-filing" information.

With regard to the allegation that the application does not disclose the induction of "mitosis or proliferation of cardiomyocytes," applicants respectfully point out that the induction of cardiomyogenesis, which is demonstrated in the application is, in fact, the mitosis or proliferation of cardiomyocytes. See, *e.g.*, the summary of methods used to assay for mitosis, *e.g.*, at pages 30-31 of the specification; and the results showing that mitosis and cell division of cardiomyocytes do, in fact, occur, *e.g.*, at pages 32-33 and the figures and table referred to therein. See also the discussion of "cardiomyogenesis" in Appendix A.

With regard to the claimed treatments of ischemic heart disease, myocardial infarction, myocardial ischemia, dilated cardiomyopathy, heart failure and hypertrophic cardiomyopathy, the demonstration in the present application of the induction of cardiomyogenesis and arteriogenesis clearly indicates that the preceding conditions can be treated by a method of the invention. These conditions exhibit shared pathophysiological features, *e.g.* myocardial cell loss (which can be treated by inducing cardiomyogenesis) and hypoperfusion (which can be treated by inducing arteriogenesis). The Examiner has failed to meet his burden to provide evidence or sound scientific reasoning as to why the indicated disease conditions can not be treated by a method of the invention.

Rejections under 35 USC 112, second paragraph

Claim 1, from which claims 2, 57 and 66 depend, has been amended to correct the typographical error, thereby obviating the rejection of claims 2, 57 and 66 as allegedly lacking antecedent basis.

Rejections (anticipation or obviousness) over Vale *et al.* (2000) *Circulation* 102, 965-974 ("Vale *et al.*")

Contrary to the allegation of the Office Action, Vale *et al.* neither anticipates nor renders obvious the instant claims.

Recognizing that the terminology related to cardiology and methods of studying heart function is rather specialized, applicants provide some non-limiting background information explaining some of the terms and methods found in Vale *et al.* and in the present application, and how they relate to the instant claims. This background information is presented as Appendix A. The literature materials from which this discussion was taken will be provided to the Examiner upon request.

This background information should aid the Examiner in recognizing that Vale *et al.*'s report that the administration of low levels of a VEGF plasmid can augment perfusion of ischemic myocardial tissue and can restore some function (as measured by LLS by the NOGA method) to the ischemic tissue is entirely different from the method of the present claims, in which the administration of an effective amount of VEGF plasmid (a significantly higher amount than that disclosed by Vale *et al.*) can actually induce cardiomyogenesis (the mitosis or proliferation of cells which can, *e.g.*, lead to the replacement of dead cells in an infarcted area). These points were presented in detail in the Reply filed June 29, 2007 and will not be repeated in the present Reply. Note in particular the discussion on page 16, second full paragraph of that Reply, which points to evidence in the application as filed that the claimed method does bring about cardiomyogenesis.

The reference does not anticipate the present claims, at least because, as was discussed in detail in the Reply filed June 29, 2007, the "effective" amount of plasmid recited in the claims is significantly higher than the amount of plasmid reported in the reference; thus, Vale *et al.*'s method to augment perfusion and restore some function to ischemic tissue would not, inherently, result in

the much more difficult task of stimulating cardiomyogenesis. In the Declaration under 37 CFR 1.132 that is attached hereto as Appendix B, Dr. Roger Laham, a respected expert in the field of cardiology and heart angiogenesis, declares that neither he nor a worker of ordinary skill, upon reading the Vale *et al.* reference, would have recognized that its method would necessarily have stimulated cardiomyogenesis. See, *e.g.*, paragraphs 8 and 10 of the Declaration. In order to inherently anticipate a claimed effect, a reference must necessarily and inevitably give rise to that effect. That is not the case here.

Furthermore, the reference does not render the present claims obvious, at least because there would have been no expectation that Vale *et al.*'s method, which augments perfusion and restores some function to ischemic tissue, would also result in cardiomyogenesis. There would have been no motivation, with a reasonable expectation of success, to try using sufficient amounts of plasmid in order to stimulate cardiomyogenesis. The stimulation of cardiomyogenesis is considerably different from merely "improving" the restoration of function to ischemic tissue by augmenting perfusion of the tissue. In support of this argument, Dr. Laham, in the attached Declaration under 37 CFR 1.132, declares that, in his opinion, the Vale *et al.* reference does not suggest or disclose that the dose of VEGF1-165 administered in the reference is effective to induce cardiomyogenesis. See, *e.g.*, paragraphs 6 and 10 of the Declaration.

Furthermore, Dr. Laham declares that it would have been unexpected at the time of filing of the application that one would be able to induce cardiomyogenesis by *any* method of gene therapy, let alone by introducing nucleic acid encoding VEGF, a protein which, until the time of the invention, was only thought to act as a growth factor for endothelial cells (not for cardiomyocytes). See, *e.g.*, paragraph 9 of the Declaration.

In further support of the non-obviousness of the present claims, it is noted that the ability to stimulate cardiomyogenesis provides advantages over the method of Vale *et al.*, in that the presently claimed method allows for the treatment of conditions that benefit from the replacement of non-viable or even lost (dead) cells, such as myocardial infarction or heart failure. See, *e.g.*, paragraph 11 of the Declaration.

In response to the allegations in the Office Action mailed October 5, 2007, applicants have the following comments:

Contrary to the allegation by the Examiner, it is not necessary to specifically recite in the broad claims that, *e.g.*, the mitotic index is increased. The increase in mitotic index is, by definition, a property associated with "cardiomyogenesis."

Furthermore, contrary to the assertion by the Examiner, Vale *et al.*'s observation that the size of the ischemic area was decreased does *not* indicate that cardiomyogenesis took place; rather, it merely shows that some cardiac function was restored to the ischemic tissue being studied, presumably by virtue of the stimulation of perfusion in the affected area. This distinction is elaborated upon in Appendix A, which provides definitions and explanations of terms and methods in Vale *et al.* and in the present application.

In the Office Action of October 5, 2007, the Examiner cites Kajstura *et al.* as allegedly showing that ischemic myocardium is *inherently* associated with cardiomyogenesis. However, the conclusions in this report have subsequently been shown to be incorrect, and to have been based on premises which were afterwards proven to be wrong. In fact, cardiomyogenesis is *not* observed in untreated ischemic tissue. The following discussion reviews these subsequent findings concerning this report by Kajstura *et al.* The relevant papers are attached.

The report by Kajstura *et al.*, as well as another report (Beltrami *et al* (2001) *N Engl J Med* 344, 1750-57) by the same group, which is headed by Piero Anversa, that cardiomyogenesis was allegedly observed in ischemic or infarcted tissue, respectively, are flawed by invalid underlying hypotheses. These incorrect underlying assumptions include that (1) the left ventricle contains  $5.8 \times 10^9$  myocytes; and (2) the duration of mitosis lasts less than one hour and equals length of cell division. The attached paper by VonHarsdorf [VanHarsdorf (2001) *Heart* 86, 481-2] points out the invalidity of these underlying hypotheses and concludes that, as of the date of its publication, the author was unaware of evidence for naturally occurring cardiomyogenesis in, *e.g.*, ischemic or infarcted tissue.

Subsequent reports have also cast doubt on the report by Anversa's group of cardiomyogenesis in ischemic or infarcted tissue. See, *e.g.*, Ahuja *et al.* (2007), *Physiol Review* 87, 521-44 (*e.g.* at page 530, column 2, first full paragraph) and Hein *et al.* (2003), *Circulation* 107, 984-91 (*e.g.* in the Abstract, last sentence of Methods and Results), which are attached.

Clearly, the Kajstura *et al.* paper cited by the Examiner does not disclose that cardiomyogenesis is present in, or is an inherent property of, ischemic or infarcted cardiac tissue.

With regard to the allegation by the Examiner that the introduction of high levels of plasmid was merely routine optimization, in order to improve the response reported in the prior art, applicants again emphasize that the induction of cardiomyogenesis is a completely different phenomenon from the recovery of function of ischemic tissue by virtue of reperfusion. The finding of cardiomyogenesis was surprising and unexpected, and there would have been no motivation to increase the dosage of plasmid in order to achieve this entirely different response. Furthermore, as discussed above, the induction of cardiomyogenesis imparted advantages that were not evident from the cited reference, further supporting the non-obviousness of the finding.

Supplementally, to further support the arguments against non-obviousness, attached as Appendix B is a Declaration under CFR 1.132 by an recognized expert in the field of cardiology and heart angiogenesis, Dr. Roger Laham, of Harvard University. In the Declaration, Dr. Laham emphasizes that the augmentation of perfusion and partial restoration of myocardial function in the affected ischemic tissue reported by Vale *et al.* following the administration of relatively low levels of VEGF plasmid is an entirely different phenomenon from the demonstration by the present inventors that administration of relatively large levels of VEGF plasmid can actually induce cardiomyogenesis (mitosis and cell proliferation). The induction of cardiomyogenesis provides an advantage in that it allows for the treatment of conditions, such as heart failure, myocardial infarction, and others, which cannot be affected by the mere restoration of cardiac activity in ischemic tissue by increased perfusion. Dr Laham declares that he, and other experts in the field at the time the invention was made, would have found the findings of the present inventors to be surprising and unexpected.

In view of the preceding arguments and amendments, it is believed that the application is in condition for allowance, which action is respectfully requested.

The Commissioner is hereby authorized to charge any fees association with this response or credit any overpayment to Deposit Account No. 22-0261, citing Docket No. 31978-193226.

Respectfully submitted,

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